the claims,[3] and invited applicants to submit a declaration. Accordingly, applicants submit herewith the Declaration of Dr. Spaete ("Spaete Decl."). Dr. Spaete is a molecular virologist and Senior Director, Research, MedImmune Vaccines, Inc.

2. REMARKS

2.1 The USPTO Did Not Apply the Correct Real-World Standard to the Vaccine Claims

It is respectfully submitted that the standard applied by the USPTO for enablement of the claimed vaccine compositions is not one that a person skilled in the art would apply. As explained by Dr. Spaete (see Spaete Decl. ¶ 4), RSV causes lower respiratory disease in pediatric and aged patients. The immunity induced by natural infection with RSV does not necessarily prevent re-infection – seasonal re-infection is a hallmark of RSV disease. As a result, the goal of an RSV vaccine is to ameliorate disease symptoms in these patients by reducing viral titer in the infected subject. (see Spaete Decl., at ¶ 4). As discussed at the interview, this is the standard applied to a number of vaccines. For example, influenza vaccines, which are produced annually, do not always completely prevent infection; nevertheless, in the industry, these compositions are still referred to as vaccines. Thus, the USPTO's requirement that vaccines must prevent infection is incorrect, and, the applicants respectfully submit that the claimed invention meets the real-world standard.

[3] Here again the applicants note a discrepancy in the standard applied to applicants' pending claims 7 and 18 versus issued claim 9 of the Conzelmann '886 patent. Conzelmann's disclosure relates to rabies virus, a member of the Rhabdovirus family, *not* the Paramyxovirus family. The Conzelmann '886 patent does not contain as much disclosure relating to the Paramyxoviruses as the present application--yet claim 9 covering such viruses was granted to Conzelmann!

2.2 The Premise for Non-Enablement is Unfounded

To support the rejection of the vaccine claims as not enabled the examiner relies on the following contentions: (1) to date, no commercial anti-RSV vaccine is available for humans (see Office Action dated June 15, 2004, at p. 4, *ll.* 14-15); and (2) applicants' data generated in animal model systems should be discounted, based on the assertion that there is no animal model system for RSV infection in humans (see Office Action dated June 15, 2004, at p. 4, *ll.* 5-7). These bases for the rejection are unfounded because, the first contention has no nexus to the success or failure of the claimed invention, and the second contention is not correct.

The delay in development of a commercial anti-RSV vaccine is not due to any failure of the technology described and claimed in the '388 application and, therefore, does not factor into an analysis of enablement of the claims. In his declaration, Dr. Spaete explains why the development of RSV vaccines was delayed and how the technology described in the '388 application overcame the problems associated with the traditional strategies for RSV vaccine development (see Spaete Decl., at ¶¶ 5 and 11). In particular, Dr. Spaete clarified that the tragic outcome of an early clinical trial conducted in the 1960s with formalin-inactivated RSV vaccines had slowed the development of RSV vaccines for decades (see Spaete Decl., at ¶ 5). In this trial, seronegative infants who were vaccinated with the formalin-inactivated vaccine went on to develop vaccine-enhanced disease during subsequent re-infection, and two infants died.

The situation changed, however, in the mid-1980s with the development of the cotton rat model for testing RSV vaccine candidates (see Spaete Decl. ¶ 6). The cotton rat models the vaccine-enhanced human disease observed with the formalin-inactivated vaccine. Indeed, the vaccine-enhanced disease observed with the formalin-inactivated vaccine human trial was reproduced in the cotton rat. As a result, the cotton rat model became the primary animal model

for testing RSV vaccine safety (see Spaete Decl., at ¶ 6). Other animal model systems were developed to test attenuation and activity of vaccine candidates (see Spaete Decl., at ¶ 7). The relative order of attenuation of different RSV mutants in these animal models is predictive of the relative order of attenuation of these RSV mutants in humans (see Spaete Decl., at ¶ 7). On the basis of their predictive value, these animal systems were (and still are) routinely used to select vaccine candidates suitable for clinical trials (see Spaete Decl., at ¶¶ 8 and 9). Indeed, results of clinical trials in human subjects showed that certain of the live attenuated mutant viruses tested met the criteria for an RSV vaccine (see Spaete Decl., at ¶ 9). Thus, animal models for human RSV disease exist, and are used routinely for evaluating vaccines.

Although the live attenuated mutant viruses tested met the criteria for vaccines, their development as commercial products was hampered because these viruses were generated by random mutagenesis – prior to the invention, they could not be generated from plasmid DNA (see Spaete Decl., at ¶ 10). The inability to rationally combine mutations and to stabilize mutations to reduce reversion rate was a problem. The advent of the technology disclosed in the present application solved this shortcoming of the prior art viruses and methods for generating recombinant viruses. The present application finally provided recombinant paramyxoviruses that could be generated from plasmid DNA, thus making paramyxoviruses amenable to the benefits of recombinant DNA technology, such as site specific mutagenesis. Thus, for the first time, mutations could be engineered into the viral genome for the rational design of vaccines. Mutations known to be attenuated in human subjects could be built into the virus, accompanied by additional mutations that prevent reversion of the attenuated phenotype to wild type (see Spaete Decl., at ¶ 11).

2.3 The '388 Application Enables the Design and Production of Infectious, Replication Competent Viruses, Including Vaccine Strains

The present application discloses different strategies to genetically modify recombinant paramyxoviruses to obtain infectious, replication competent viruses. Expression levels of viral genes can be altered by "gene shuffling" or changes to the intergenic regions of the viral genome (see Spaete Decl., at ¶ 12). This "gene shuffling" approach is an example of how the specification not only provides guidance for how to modify the viral genome but also teaches the effect such a modification will have; due to the 3' to 5' transcriptional gradient, translocation of a viral gene to a more 3' location will increase and to a more 5' location will decrease expression of the translocated gene (see Spaete Decl., at ¶ 12).

The present application further teaches which genes of the viral genome can be targeted by genetic modifications, such as insertions, deletions, and substitutions (see Spaete Decl., at ¶ 13). The effects of these modifications on the modified virus are also taught in the specification (see Spaete Decl., at ¶ 13). In addition, the application discloses different strategies for the modification of viral proteins (see Spaete Decl., at ¶ 14). These strategies include (i) the removal of charges from a viral protein to affect the protein's function without grossly altering its structure, and (ii) cysteine scanning mutagenesis to alter the tertiary structure of a viral protein (see Spaete Decl., at ¶ 14). Recombinant RSV in which charges had been removed from the L protein were indeed rescued and shown to be infectious and replication competent. Like the substitutions used in the working examples to remove charges from the L protein, replication competent paramyxoviruses can be constructed with deletions of amino acids from the L protein (see Spaete Decl., at ¶ 20).

The present application further discloses that routine assays can be used to evaluate the impact of the genetic modifications on the virus. Such assays can be performed to assess the function of individual mutated viral proteins using a minigenome replication system or the function of the assembled viral mutant (see Spaete Decl., at ¶ 15). The skilled artisan was prepared to use such routine experimentation to identify viral mutants that are infectious and replication competent, or, for purposes of vaccine development, attenuated (see Spaete Decl., at ¶ 22).

A case in point, is *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). In *Wands*, antibodies that were required to perform the claimed immunoassays were held to be enabled even though only a small percentage of hybridomas were proved to fall within the claims. *Id.* at 739. In *Wands* routine assays could be used to identify the suitable hybridomas. Similarly, in the present situation, routine assays can be used to identify among the genetically modified recombinant viruses of the invention, those that are infectious and replication competent. In contrast to *Wands*, however, where hybridomas were generated randomly, the present specification even provides guidance for the rational design of modifications that affect different aspects of the recombinant virus (see Spaete Decl., at ¶¶ 12, 13, and 14). Thus, the present application not only meets but even exceeds the legal standard for enablement.

The present application does not stop at providing guidance with respect to the modifications that can be introduced into recombinant paramyxoviruses to obtain infectious, replication competent viruses; the present application also provides numerous working examples to demonstrate that the guidance taught can indeed be realized to generate infectious, replication competent virus (see Spaete Decl., at ¶¶ 16, 17, 18, and 19). These working examples illustrate modifications as diverse as deletions of entire open reading frames (see Spaete Decl., at ¶¶ 17

and 18), insertions of entire open reading frames (see Spaete Decl., at ¶ 19), substitutions of entire open reading frames (see Spaete Decl., at ¶ 19), and removal of charges from a viral protein (see Spaete Decl., at ¶ 16). Indeed, other research groups that generated similar viral mutants in paramyxoviruses, such as RSV, PIV, and hMPV, also obtained infectious, replication-competent viruses (see Spaete Decl., at ¶¶ 21 and 23), thus demonstrating that the teachings and guidance provided by the present application are generally applicable to paramyxoviruses (see Spaete Decl., at ¶ 21). Some of these viral mutants have since also been shown to be attenuated indicating that these viral mutants are suitable as vaccines (see Spaete Decl., at ¶¶ 21 and 23). Further, applicants' RSV mutants are active in the very same animal models that were used to select vaccines for clinical trials (see Spaete Decl., at ¶¶ 17 and 18).

For all the foregoing reasons the claims are enabled. The Spaete Declaration provides factual support that the claimed viruses and vaccines are enabled. In the event the examiner disagrees, and to the extent that any rejection is based on facts within his personal knowledge, applicants request that the examiner provide an affidavit pursuant to the provisions of 37 C.F.R. 1.104(d)(2).

3. Miscellaneous

Claims 13-16, which are directed to methods for rescuing virus are withdrawn as a result of the Restriction Requirement dated November 19, 2002 ("Restriction Requirement"). In particular, these method claims were restricted out because these claims are not limited to paramyxoviruses but instead are directed to non-segmented negative-stranded RNA viruses (see the Restriction Requirement dated November 19, 2002, the paragraph spanning pages 2 and 3).

Claim 14, however, is limited to paramyxoviruses from plasmid DNA.[4] Because the reasoning set forth in the Restriction Requirement does not apply to claim 14, claim 14 and its dependent claims (claims 15 and 16) should be examined together with the pending claims. Applicants respectfully point out that the rejections against the pending composition and vaccine claims are inapplicable to the method claims. The method claims are directed to a new way of rescuing paramyxoviruses, including wild-type viruses, from plasmid DNA. These methods can be practiced by the skilled artisan without regard to any modifications that are engineered into the viral genome. Thus, the examiner's argument that the specification does not provide enough guidance to make paramyxoviruses with certain specified characteristics would not apply to the methods for making paramyxoviruses.

Assuming the USPTO is in agreement, and in order to expedite prosecution, Applicants would be willing to amend claim 13 to incorporate the limitation of claim 14 that the virus is a paramyxovirus.

4. CONCLUSION

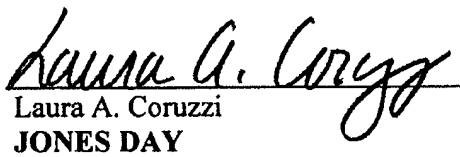
Applicants respectfully request that the present remarks be entered and made of record in the instant application. An allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

[4] In fact, claim 14 in the present application corresponds to claim 17 in the Conzelmann '886 patent, where the composition claims were examined together with the method claims.

No fee is believed to be required for this response. However, should any fee be due, please charge the required amount to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date October 4, 2005



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